



## First licensed veterinary medicine composed of equine umbilical cord mesenchymal stem cells (EUC-MSC)

### Introduction osteoarthritis and treatment options

Osteoarthritis (OA) is a chronic, degenerative inflammatory process in the joints involving damage to cartilage and abnormal bone growth. It is a major cause of lameness in horses; in some studies, 60% of lameness's could be related to OA.

Several causes are known, in which overuse and conformational inadequacies leading to improper loading of the joint play a major role. OA can occur suddenly due to trauma, for example, but can also develop over a longer period of time.

Inflammation often starts in the synovium, cartilage, joint capsule or subchondral bone. From this initial process, an inflammatory cascade starts, leading to the inflammation of secondary tissues from which new inflammatory mediators are released. This vicious cycle eventually leads to a dysregulation between the catabolic and anabolic processes in the joint causing cartilage degeneration. The inflammatory response in the joint is a key component in the development of OA.

Simultaneous synovitis is an important component in the disease process. Activated macrophages and lymphocytes in the synovium secrete inflammatory cytokines such as IL-1, IL-6 and TNF-alpha. Due to the influence of these cytokines, cartilage matrix homeostasis is impaired and metalloproteases are released, which damage the chondrocytes and cartilage. The released components of the cartilage matrix stimulate inflammatory responses, further intensifying inflammation. The subchondral bone responds to cartilage loss by forming bone, causing irreversible changes in the joint.

The processes in the joint can manifest themselves in clinical symptoms of inflammation: heat, swelling, pain, lameness, and reduced range of motion of the joint. Deformations at the joint and crepitus may also be observed at clinical examination.

Treatment of osteoarthritis often aims to reduce inflammation and control pain. This is achieved by treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular corticosteroids (COs). Nowadays, an increasing number of therapies are applied that are intended to affect cartilage metabolism and joint function, such as hyaluronic acid (HA), polysulphated glycosaminoglycans (PSGAG) and pentosanpolysulphate.



In recent years, an increasing focus has been on orthobiologics, which are biological substances used to treat orthopaedic conditions. In OA, autologous substances such as autologous protein solution (APS) or stem cells from bone marrow are used, for example. Allogeneic orthobiologics, obtained from other horses, in OA include stem cells.

### HorStem umbilical cord mesenchymal stem cells mechanism of action

Umbilical cord mesenchymal stem cells are activated in the synovium by inflammatory cytokines, in response they secrete anti-inflammatory cytokines such as Prostaglandin E2 (PGE2). Although PGE2 is mostly known for its pro-inflammatory influence, it also has an important role in regulating inflammation. It is known as one of the greater immunomodulatory cytokines in the body.

The application of umbilical cord mesenchymal stem cells in horses with OA inhibits T-cell proliferation, the production of pro-inflammatory cytokines such as TNF-alpha and reduces the presence of matrix metalloproteases (MMP) that cause degradation of the extracellular matrix of cartilage. Studies have shown that these effects are mediated by PGE2. Umbilical cord mesenchymal stem cells also stimulate the production of anti-inflammatory cytokines such as IL-4, IL-5, IL-10 and TGF-beta.

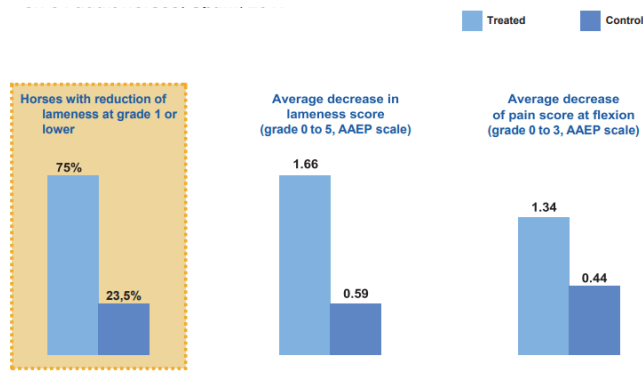
As the inflammatory response ends and the amount of MMP decreases, cartilage destruction and disease progression will stop. Stem cells create the ideal environment for tissue regeneration. The inflammatory symptoms and associated lameness will also resolve.



**Clinical study HorStem**

A comparative superiority, multicentric, parallel, blinded, randomized and placebo-controlled clinical trials were performed. Horses were randomly assigned to receive a treatment with HorStem (N=36) or a placebo containing saline solution (N=39). The horses were evaluated based on lameness grades, joint effusion and flexion pain. Additionally subjective improvement observed by the veterinarian and the owner were taken into account.

The group treated with Equine Umbilical Cord Mesenchymal Stem Cells showed a greater reduction in lameness score and pain score compared to the placebo group. In addition, 75% of horses treated with Equine Umbilical Cord Mesenchymal Stem Cells had lameness scores reduced to an AAEP score of 1 or lower (non-lame or inconsistent lameness) by day 63.



The study showed that clinical improvement persisted for more than a year in 84% of the treated horses.

**Instructions**

HorStem is a sterile injectable suspension for horses 1ml vial containing 15-million cells per dose, it is delivered and stored refrigerated. Swirl the product gently before administration to mix the contents well.

Administer a single intra-articular injection of 1 ml into the affected joint, using a 20G needle. The product should be inserted sterile and treatment should take place in a clean environment.

HORSTEM PRODUCT INFORMATION	
Brand	EquiCord
Target species	Horses
Veterinary use	To be supplied only on veterinary prescription
Storage	2 °C - 8 °C
Withdrawal period	0 days
Marketing authorization number	EU/2/18/226/001
Package	Cardboard box with 1 vial containing 1 ml
Article code	Nr. 119563 - HorStem 1ml

**References**

Goodrich LR, Nixon AJ. Medical treatment of osteoarthritis in the horse—a review. The Veterinary Journal. 2006 Jan 1;171(1):51-69.

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McIlwraith CW, Frisbie DD, Kawcak CE. The horse as a model of naturally occurring osteoarthritis. Bone & joint research. 2012 Nov;1(11):297-309.